World Health Organization

WHO R&D Blueprint

COVID-1

Informal consultation on the potential role of chloroquine in the clinical management of COVID 19 infection

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R&DBlueprint

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Appropriate WHO Confidentiality Undertakings were signed and submitted to WHO by all participating experts

INTRODUCTION

Currently, there are no therapeutic agents licensed and available for the treatment of COVID 19. On the 27th of January, WHO convened a meeting of experts to examine the available evidence and prioritize promising therapeutic agents for further evaluation in the ongoing outbreak. The expert panel recommended the direct-acting antiviral agent, Remdesivir, and the protease inhibitor, Lopinavir/ritonavir for evaluation in randomized clinical trials. At the time, there was insufficient evidence to support chloroquine's further investigation. However, chloroquine has received significant attention in countries as a potentially useful prophylactic and curative agent, prompting the need to examine emerging evidence to inform a decision on its potential role. At the time of convening this meeting, about 500 clinical trials were ongoing in China, with at least 13 evaluating chloroquine's efficacy.

This expert consultation convened clinical care partners and experts in the field of randomized controlled trials (RCTs), preclinical studies, and chloroquine pharmacology for evaluating newly available evidence.

OBJECTIVES OF THE CONSULTATION

The objectives of this consultation were:

1. To review and critically appraise the existing evidence regarding chloroquine and hydroxychloroquine;

2. To decide on the further evaluation of chloroquine- based on currently available evidence – in humans infected with SARS-CoV-2 to reduce mortality and disease progression.

This Consultation represents an initial step towards the evaluation of chloroquine against the SARS-CoV-2. There are ongoing efforts to identify additional candidate therapeutics and to expand the body of evidence available on each of the candidates.

Agenda items

- Introduction and roll-call.
- Update on current evidence on chloroquine.
- Conclusions and next steps.

Participants

Chair: Marco Cavaleri

Name	Position	Institutional Affiliation
Marco Cavaleri	Head of Anti-infectives and Vaccines	European Medicines Agency, Netherlands
Eric Pelfrene	Office of Anti-infectives and Vaccines	European Medicines Agency, Netherlands
Sina Bavari	Independent Consultant	
Karl Erlandson	Interdisciplinary Scientist	Biomedical Advanced Research and Development Authority,

Name	Position	Institutional Affiliation
		US Department of Health and Human Services
Yaseen Arabi	Chairman, Intensive Care Department	King Saud bin Abdulaziz University for Health Sciences, Riyadh, Saudi Arabia
John Marshall	Co-Director, Critical Illness and Injury Research Centre, St Michael Hospital, Canada	Co-Director, Critical Illness Research, St Michaels Hospital
Ross Upshur	Director, Primary Care Research Unit, Sunnybrook and Women's College Health Sciences Centre, Canada Research Chair in Primary Care Research	University of Toronto, Canada
John Beigel	Associate Director for Clinical Research	NIH, USA
Thomas Fleming	Professor of Biostatistics	University of Washington
John Farley	Director, Office of Infectious Diseases	FDA, USA
Philip Krause	Deputy Director CBER/OVRR	FDA, USA
Regine Lehnert	Doctor	Federal Institute for Drugs and Medical Devices, Germany
Monalisa Chatterji	Senior Program Officer, Discovery & Translational Science	Bill & Melinda Gates Foundation, USA
Michael Kaufmann	Manager- Advisory	PriceWaterhouse Cooper,USA

Name	Position	Institutional Affiliation
David Vaughn	Senior Program Officer	Bill & Melinda Gates Foundation, USA
Ken Duncan	Discovery & Translational Sciences team Lead	Bill & Melinda Gates Foundation, USA
Nicholas White	Professor of Tropical Medicine	Mahidol University, Thailand
Robert Walker	Chief Medical Officer and Director, Division of Clinical Development	Biomedical Advanced Research and Development Authority, US Department of Health and Human Services
Julia Tree	Microbiological Services	Public Health England
Scott Miller	Deputy Director, medical interventions	Bill & Melinda Gates Foundation, USA
Frederick Hayden	Professor Emeritus, Medicine: Infectious Diseases and International Health	University of Virginia
Jacqueline Kirchner	Senior Program Officer	Bill & Melinda Gates Foundation, USA
Elizabeth Higgs	Global health science advisor for the Division of Clinical Research (DCR)	NIH. USA
Helen Rees	Professor, Wits Reproductive Health and HIV Institute	University of Witwatersrand, South Africa
Matthew Frieman	Associate Professor, Microbiology and Immunology	University of Maryland School of Medicine

Other invited experts but only those listed in the table above participated: Hilary Marston (US NIH), Philip Coyne (US PHS), Sina Bavari (Independent consultant), Marco Cavaleri (EMA), Jeremy Farrar (Wellcome Trust, UK), Markus Mueller (University of Wien), Bin Du (Peking), Yi Guan (Hong Kong); Wannian Liang (MOH China), Bruno Lina (France), Claire Madelaine William Dowling (CEPI, USA)

WHO Secretariat: Alejandro Costa, Janet Diaz, Ana Maria Henao-Restrepo, Marie-Pierre Preziosi, Vasee Moorthy, Ximena Riveros Balta, Kolawole Salami, Emer Cooke, Deusdedit Mubangizi, Matthias Mario Stahl, and Pierre Gsell.

OVERVIEW OF THE DELIBERATIONS

Overall considerations

- Chloroquine has shown in vitro activity against some viruses, including chikungunya, dengue, and influenzas, but in vivo studies in animal models and randomized controlled trials (RCTs) in humans have been largely disappointing. Chloroquine pre-treatment (prophylaxis) was associated with an enhancement of viral replication and disease with chikungunya in NHPs due to delays in immune responses. Chloroquine treatment of chikungunya infection in humans did not affect viremia or clinical parameters during the acute stage of the disease. However, it reduced levels of C-reactive Protein (CRP) and specific cytokines.

- Chloroquine is reasonably active in vitro against SARS-CoV, MERS CoV, and SARS-CoV-2, the causative agent of COVID 19. In vitro studies have shown antiviral activity with an EC50 of 1.0 -1.5 µmolar in Vero cells, but it is unclear how this translates into activity in respiratory epithelial cells and in vivo. BMGF has developed a model of chloroquine penetration into tissues for malaria. This model indicates that the concentration seen in the plasma is similar to that achieved in the lungs, and even when the concentration is below the IC50 in the plasma, there could be the desired reasonable concentration in the lungs. This model is, however, not validated. Chloroquine also has the attraction of

being relatively safe, well-tolerated, and cheap to produce. Hence, it is essential to explore further its possibilities as a therapeutic agent for COVID 19.

- The selective index of chloroquine and chloroquine diphosphate for SARS-CoV in African Green Monkey kidney cells was low, ranging from 5-13 for a laboratory strain and 2-20-fold for four clinical strains (Barnard, 2006) and this should be a cause for concern. Also, intraperitoneal delivery of chloroquine starting 4 hours before viral challenge did reduce lung titres of SARS-CoV.

- A recent in vitro study shows hydroxychloroquine to have greater antiviral activity against SARS CoV-2 in Vero cell lines than chloroquine. However, another recently published RCT study in China with hydroxychloroquine involving 30 COVID 19 patients with mild to moderate symptoms shows no significant reduction in time to clinical improvement or viral clearance in the hydroxychloroquine arm compared to the conventional therapy control group.

- An experiment in murine models with SARS-CoV (MA15) in BALB/c mice and MERS-CoV (in the Ad5/hDPP4 mouse model) at the University of Maryland School of Medicine, involving the daily administration of 40ml/kg and 80 ml/kg dose of chloroquine resulted in protection from weight loss, lung pathology, and clinical symptoms but no reduction in viral titters. Further experiments to delineate the antiviral and immunomodulating effects are ongoing.

- A placebo-controlled trial of longer-term chloroquine prophylaxis is currently being planned and could commence as early as two weeks. The study would involve 20,000 healthcare workers. For this study, chloroquine will be tested daily as used in the treatment of rheumatoid arthritis. A loading dose of 10 mg base/kg, followed by 100 mg daily, will be taken for three months or until they are diagnosed with COVID-19. Higher doses would be considered for treatment, i.e., 10mg/kg base, followed by 5mg/kg twice daily for seven days. BMGF is also developing a post-exposure prophylaxis clinical trial protocol for hydroxychloroquine that would be made available next week. No prophylactic trials involving chloroquine have been reported from in China.

Conclusions:

- It is expected that there would be some results from animal model studies involving chloroquine in the coming days. However, the decision about the global clinical trial protocol needs to be made ASAP, and WHO would appreciate the possibility of taking this decision from this panel discussion if possible. WHO to contact colleagues from NIH and animal model group to determine the type of animal studies ongoing and the dose of chloroquine being used.

- Both post-exposure prophylaxis and longer-term prophylactic use of hydroxychloroquine & chloroquine should also be considered.

- BMGF and other global health partners are developing protocols for this prophylactic use. Since WHO also has a prophylaxis protocol, and all must work in unison and avoid duplicate efforts. WHO has proposed a TC involving partners working on prophylaxis to have a common approach. The date and time will be communicated soon by WHO.

- There are more than 20 treatment studies ongoing in China utilizing chloroquine, and it would be better to get these data, provided studies design allows interpretation of data, rather than wait for animal studies from the NIH. WHO is engaging with Chinese colleagues at the mission in Geneva and have received assurances of improved collaboration; however, no data has been shared regarding the chloroquine studies. It should be noted that the RCTs in China are small and may not be powered enough to reach the conclusions that are needed.

- Animal studies could be useful to conclude that there are no disease enhancement signals, but making firm conclusions about clinical efficacy is uncertain. It should be possible to assess antiviral efficacy in animal models, but the immunomodulatory effects of chloroquine will depend on the pathogenesis of the model. Current limited evidence from preclinical studies

with coronaviruses would not suggest a scenario similar to what was observed with chikungunya. Moreover, it would not be expected that the data from the ongoing animal studies would provide definitive findings before proceeding to clinical evaluation.

PROPOSED NEXT STEPS

- As the decision should be taken rapidly based on available data, it was agreed that there is equipoise for the inclusion of chloroquine in clinical trials and to proceed with the evaluation of chloroquine in COVID 19 patients.

- Members of the expert panel were invited to share with the WHO R&D Blueprint any additional information on chloroquine that should be considered.

- The panel will be convened again in a week to discuss the various protocols available for the evaluation of chloroquine's efficacy as a pre or post-exposure prophylaxis agent in COVID 19, and to align efforts for maximal synergy.

Note that above prioritization decisions are preliminary and may change as further information is provided to WHO.